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The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma

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Zürich and Basel, Switzerland; Sydney, Australia; Hannover, Jena, Gera, Mainz, Münster, and Berlin, Germany; Antwerp and Brussels, Belgium; Aurora, Colorado; Lyon, France; Glasgow, Newcastle upon Tyne, and Manchester, United Kingdom; Athens, Greece; East Hanover, New Jersey; Redwood City, California; Atlanta, Georgia; and Houston, Texas

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Background: The hedgehog pathway inhibitor sonidegib demonstrated meaningful tumor shrinkage in more than 90% of patients with locally advanced basal cell carcinoma (BCC) or metastatic BCC in the BCC Outcomes with LDE225 Treatment study.

Objective: This report provides long-term follow-up data collected up to 12 months after the last patient was randomized.

Methods: In this multicenter, randomized, double-blind phase II study, patients were randomized 1:2 to sonidegib 200 or 800 mg. The primary end point was objective response rate assessed by central review.

Results: Objective response rates in the 200- and 800-mg arms were 57.6% and 43.8% in locally advanced BCC and 7.7% and 17.4% in metastatic BCC, respectively. Among the 94 patients with locally advanced BCC who responded, only 18 progressed or died and more than 50% had responses lasting longer than 6 months. In addition, 4 of 5 responders with metastatic BCC maintained an objective response. Grade 3/4 adverse events and those leading to discontinuation were less frequent with sonidegib 200 versus 800 mg (38.0% vs 59.3%; 27.8% vs 37.3%, respectively).

Limitations: No placebo or comparator arms were used because sonidegib demonstrated efficacy in advanced BCC in a phase I study, and the hedgehog pathway inhibitor vismodegib was not yet approved.

Conclusion: With longer follow-up, sonidegib demonstrated sustained tumor responses in patients with advanced BCC. (J Am Acad Dermatol 2016;75:113-25.)

Key words: advanced basal cell carcinoma; Basal Cell Carcinoma Outcomes with LDE225 Treatment study; hedgehog pathway inhibitor; locally advanced basal cell carcinoma; metastatic basal cell carcinoma; sonidegib.

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Basal cell carcinoma (BCC), the most commonly diagnosed cancer,[1,2] is associated with aberrant activation of hedgehog signaling caused by sporadic mutations in the pathway components patched (>85% of cases) and smoothened (≈10%).[3-5] The vast majority of BCCs are effectively treated with topical therapy, surgery, and/or radiotherapy,[6-8] but in a minority (<1%) of patients, BCCs can become advanced and difficult to treat.[9] For patients with advanced BCC, including those with locally advanced BCC (laBCC) who may have multiple, large, neglected, poorly defined, aggressive, and/or recurrent lesions that are not amenable to surgery/radiation and those with metastatic BCC (mBCC), treatment options are limited[1,10] and include the oral hedgehog pathway inhibitors (HPIs) sonidegib and vismodegib,[11-17] more conventional chemotherapy, radiation (mBCC), or a clinical trial.[6-8]

CAPSULE SUMMARY

- Hedgehog pathway inhibition is one of the few treatment options available for patients with advanced basal cell carcinoma.
- Sonidegib provides meaningful tumor shrinkage and durable responses in patients with advanced basal cell carcinoma.
- Sonidegib may offer a promising new treatment option for this difficult-to-treat patient population.

Sonidegib (LDE225) is an oral HPI that selectively targets the pathway activator smoothened, thereby inhibiting hedgehog pathway signaling.[18,19] Sonidegib (200 mg) was approved for use in patients with advanced BCC[11,12] or laBCC[13,14] who are not amenable to curative surgery/radiotherapy based on the meaningful, durable tumor responses observed in the BCC Outcomes with LDE225 Treatment (BOLT) study.[20] The primary end point, objective response rate (ORR), was met in both treatment arms at the time of the primary analysis (June 28, 2013, cutoff).[20] Updated safety and efficacy data from the 12-month analysis (December 31, 2013, cutoff) are presented.

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Supplemental tables and figures are available at http://www.jaad.org.

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Abbreviations used:

BCC:	basal cell carcinoma
BOLT:	Basal Cell Carcinoma Outcomes with LDE225 Treatment
HPI:	hedgehog pathway inhibitor
laBCC:	locally advanced basal cell carcinoma
mBCC:	metastatic basal cell carcinoma
mRECIST:	modified Response Evaluation Criteria in Solid Tumors
ORR:	objective response rate
RECIST:	Response Evaluation Criteria in Solid Tumors
WHO:	World Health Organization

METHODS

Trial design and patient eligibility

BOLT, a multicenter (58 centers, 12 countries), randomized, double-blind, phase II study (NCT 01327053), evaluated once-daily doses of sonidegib 200 or 800 mg.[20] Adults with either histologically confirmed laBCC not amenable to radiotherapy or curative surgery or mBCC, who had adequate organ function and a World Health Organization (WHO)[21] performance status less than or equal to 2, were eligible. Patients previously treated with HPIs were excluded.

Patients were randomized 1:2 to the 200-mg (lowest efficacious dose[19]) and 800-mg (highest well-tolerated, once-daily dose[19]) treatment arms based on the prediction that the 800-mg dose would be more efficacious: phase I data indicated dose- and exposure-dependent inhibition of glioma-associated oncogene-1 (biomarker for hedgehog pathway activity).[19] Patients were stratified based on disease (laBCC vs mBCC), histologic subtype for laBCC (aggressive vs nonaggressive), and geographic region. Patients were randomized by an independent provider using the central Interactive Response Technology system (Cenduit, Allentown, PA), and all involved in the study were blinded until the time of the primary analysis.[20] The independent ethics committee or institutional review board for each center approved the study protocol, and each patient provided informed consent before enrollment.

Outcomes

The primary end point was ORR—proportion of patients with a best overall response of complete or partial response—per central review. Secondary end points included ORR by investigator review; complete response rate, time to tumor response, duration of response, and progression-free survival by central and investigator review; and safety. End points were assessed using data collected up to 12 months after the last patient was randomized.

Study intervention and assessments

Patients were treated with sonidegib on a once-daily continuous schedule until disease progression, intolerable toxicity, withdrawal of consent, death, discontinuation, or study termination. Tumor assessments were performed at baseline, during treatment/posttreatment follow-up (weeks 5 and 9, followed by every 8 weeks during year 1, and every 12 weeks thereafter), and at discontinuation according to BCC-modified Response Evaluation Criteria in Solid Tumors (mRECIST) for laBCC and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[22] for mBCC. Complete and partial responses required confirmation on repeated assessments at visits greater than or equal to 4 weeks apart. The potential for posttreatment ulceration, cyst formation, scarring/fibrosis, and ill-defined lesion borders renders RECIST v1.1[22] inadequate for tumor assessment in patients with laBCC. BCC-mRECIST is a stringent composite multimodal assessment tool that integrates magnetic resonance imaging per RECIST v1.1[22] (response: ≥30% reduction in the sum of longest diameters of target lesions), standard and annotated color photography per bidimensional WHO guidelines[21] (response: ≥50% reduction in the sum of products of perpendicular diameters of target lesions), and histology in multiple biopsy specimens surveying the lesion area (Supplemental Table I). An independent review committee reevaluated all central assessments for laBCC. Fresh tumor biopsy specimens were required to confirm a complete response and/or when assessment was confounded by ulceration, cyst formation and/or scarring/fibrosis. Adverse events were monitored according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03[23] from the start of study treatment until 30 days after the last dose of sonidegib.

Statistical methods

ORR and complete response rate with 95% confidence intervals were estimated by treatment arm and disease (laBCC or mBCC). Kaplan-Meier nonparametric maximum likelihood estimate of median time and 95% confidence intervals were calculated for duration of response, time to tumor response, and progression-free survival by treatment arm and disease. Statistical testing to compare the 200- and 800-mg arms was not planned. Detailed statistical methods of the primary analysis were previously reported.[20]

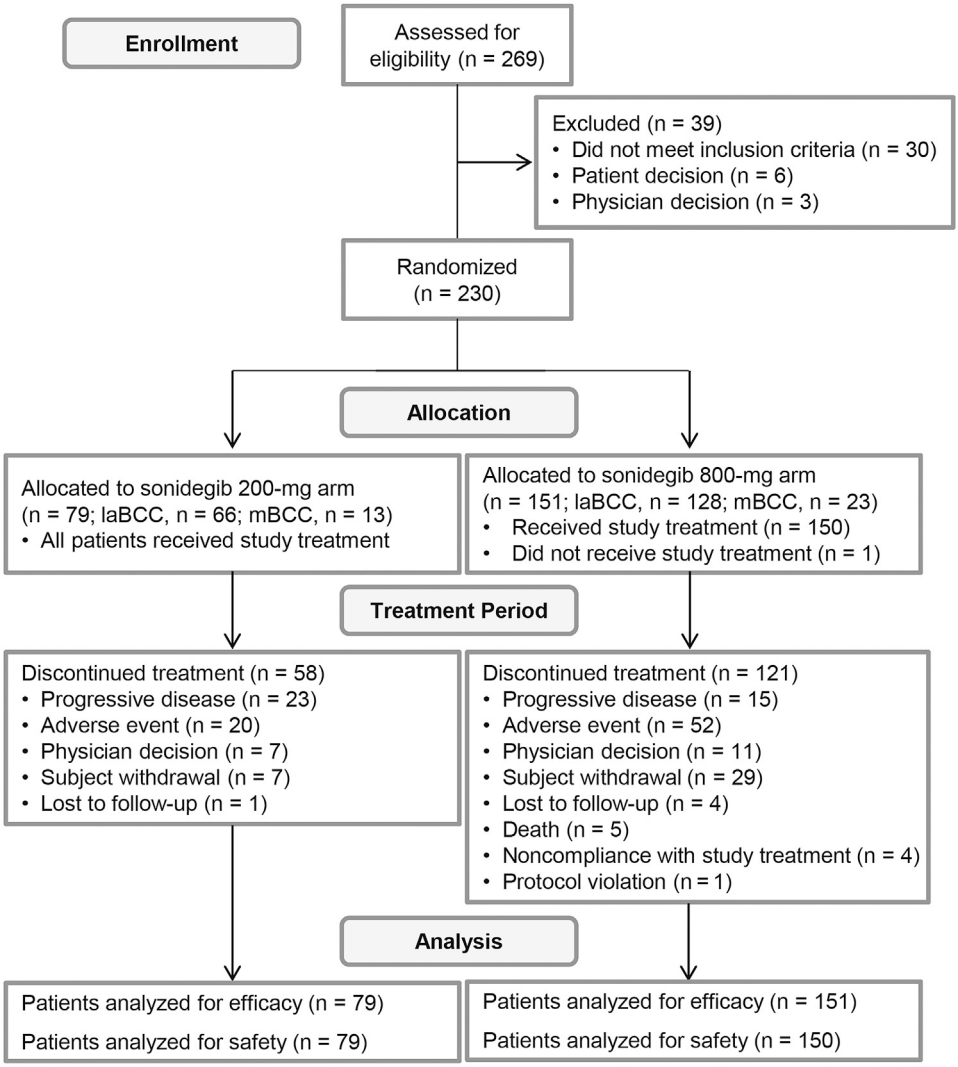

Fig 1. A total of 230 patients with advanced basal cell carcinoma (BCC) were randomized to receive once-daily doses of sonidegib 200 mg (n = 79; locally advanced BCC [laBCC], n = 66; metastatic BCC [mBCC], n = 13) or 800 mg (n = 151; laBCC, n = 128; mBCC, n = 23). All randomized patients were assessed for efficacy. One patient in the sonidegib 800-mg arm did not receive treatment and therefore was not included in the safety analysis.

RESULTS

Patient baseline characteristics, disease history, and disposition

A total of 230 patients (laBCC, n = 194; mBCC, n = 36) enrolled in BOLT between July 20, 2011, and January 10, 2013, were randomized into the sonidegib 200-mg (n = 79) or 800-mg (n = 151) treatment arms (Fig 1). Baseline patient demographics and disease history were similar between arms (Supplemental Table II).[20] Tumor burden at baseline was extensive, with 62.2% of patients having 2 or more lesions. At data cutoff for the 12-month analysis (December 31, 2013), 77.8% of patients (73.4% vs 80.1% [200- vs 800-mg]) had discontinued treatment, largely because of adverse events (25.3% vs 34.4%), progressive disease (29.1% vs 9.9%), or patient decision (8.9% vs 19.2%) (Supplemental Table III); most discontinuations because of patient and physician decision were because of adverse events.

Efficacy in patients with laBCC

Efficacy in patients with laBCC in the 12-month analysis was generally similar to or improved from that observed in the primary analysis (Figs 2 to 4; Supplemental Fig 1; and Table I).[20] Response rates (percentage of complete and partial responses) per central review were 57.6% and 43.8% in the 200- and 800-mg arms, respectively (Fig 2, *A*). Investigator-reported response rates were higher than those reported by central review (Fig 2, *B*). Disease control

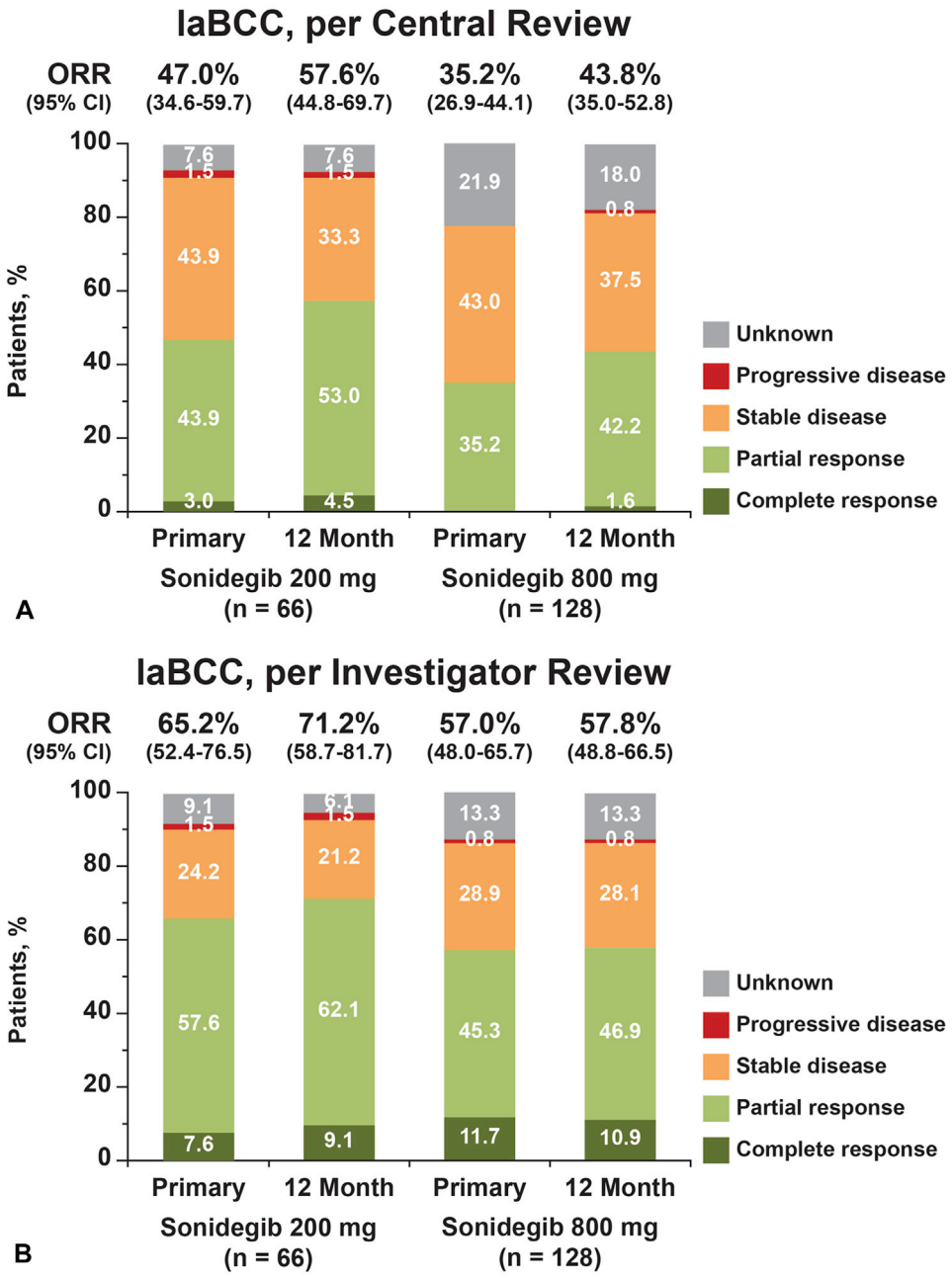

Fig 2. Objective response rates (ORRs) in patients with locally advanced basal cell carcinoma (laBCC) treated with sonidegib 200 and 800 mg. Best overall response in patients with laBCC treated with sonidegib 200 mg (n = 66) and 800 mg (n = 128) assessed by photography, magnetic resonance imaging, and histology according to basal cell carcinoma–modified Response Evaluation Criteria in Solid Tumors by central (**A**) and investigator (**B**) review at the time of the primary and 12-month analyses. Complete and partial responses required confirmation on repeated assessments at visits greater than or equal to 4 weeks apart and biopsy specimens were required to confirm a complete response.

rates (percentage of complete responses, partial responses, and stable disease) were greater than 90% with sonidegib 200 mg (central, 90.9%; investigator, 92.4%) and more than 80% with sonidegib 800 mg (central, 81.3%; investigator, 85.9%). Tumor shrinkage (percentage of patients with a reduction in the sum of the measurements of target lesion[s] per photograph any time before data cutoff) by central review was observed in 92.3% (Fig 3, *A*) and 90.1% (Supplemental Fig 1, *A*) of patients treated with sonidegib 200 and 800 mg, respectively; investigators reported similar results (Supplemental Fig 1,

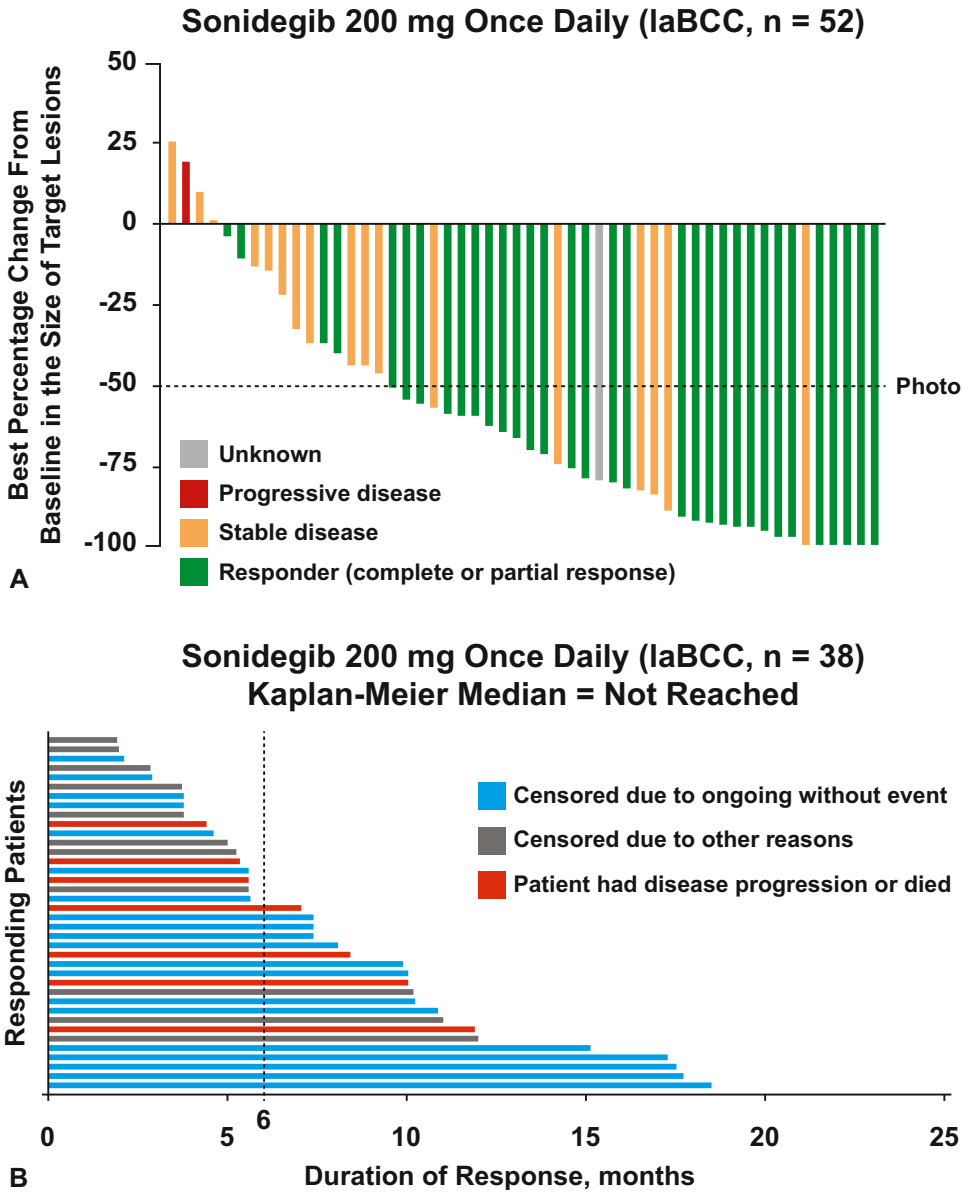

Fig 3. Waterfall plots of best change from baseline in the size of target lesions and of duration of response in patients with locally advanced basal cell carcinoma (laBCC) per central review. Best percentage change from baseline in the sum of the products of perpendicular diameters in target lesion(s) assessed by photography per World Health Organization criteria[21] per central review (**A**). Tumor response was assessed by photography, magnetic resonance imaging, and histology according to basal cell carcinoma–modified Response Evaluation Criteria in Solid Tumors in patients with laBCC, and best overall response is depicted by color. Assessments were excluded from the analysis if percentage change in the size of target lesions was not available or was contradicted by an overall lesion response of unknown. Duration of response by patient evaluated by central review in patients responding to treatment with sonidegib 200 mg (**B**).

B and *C*). Median time to tumor response in the 200- and 800-mg arms was 4.0 and 3.8 months by central review and 2.5 and 1.9 months by investigator review, respectively (Table I). Of 94 patients (200 mg, n = 38; 800 mg, n = 56) who responded (central review), only 18 (19.1%; 200 mg, n = 7; 800 mg, n = 11) had disease progression or died (Table I). The Kaplan-Meier median duration of response by central review was not reached with 200 mg, because few responders had disease progression or died, and was 15.7 months with 800 mg; respective median durations of response by investigator review were 20.2 and 19.8 months (Table I). Responses lasting more than 6 months by

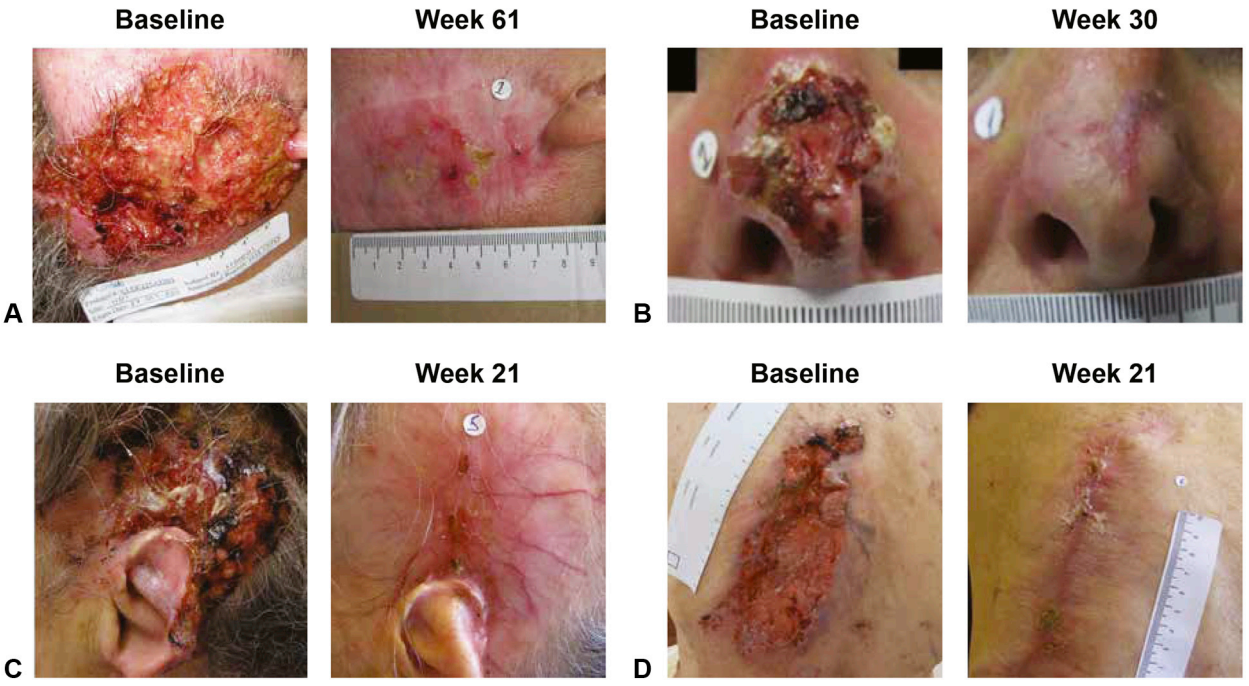

Fig 4. Images of tumor response in patients with locally advanced basal cell carcinoma (laBCC) treated with sonidegib. **A**, Cheek of a 49-year-old white male patient with aggressive laBCC treated with sonidegib 200 mg at baseline and week 61. This patient achieved an overall partial response by central and investigator review. **B**, Nose of a 45-year-old white female patient with aggressive laBCC treated with sonidegib 800 mg at baseline and week 30. This patient achieved an overall response of stable disease by central and investigator review. A partial response was reported at the end of treatment on day 221. Left scalp (**C**) and back (**D**) of a 78-year-old white female patient with aggressive laBCC treated with sonidegib 800 mg (baseline and week 21). This patient, who remained on treatment for 590 days, achieved an overall partial response per central and investigator review.

central review were observed in 52.6% and 53.6% of responders treated with 200 mg (Fig 3, *B*) and 800 mg (data not shown), respectively.

Among patients with laBCC, 56.1% and 58.6% had aggressive histologic subtypes of BCC (ie, micronodular, infiltrative, multifocal, basosquamous, or sclerosing) based on randomization stratification in the 200- and 800-mg arms, respectively; nonaggressive subtypes included nodular and superficial BCCs. Response rates in patients with aggressive versus nonaggressive subtypes per central review were 59.5% versus 55.2% in the 200-mg arm and 44.0% versus 43.4% in the 800-mg arm, respectively; per investigator review, the respective response rates were 70.3% versus 72.4% (200 mg) and 54.7% versus 62.3% (800 mg).

Efficacy in patients with mBCC

In the 12-month analysis, efficacy in patients with mBCC was generally similar to that observed in the primary analysis (Fig 5; Supplemental Fig 2; and Table I).[20] Response rates in patients with mBCC by central review were 7.7% and 17.4% in the 200- and 800-mg arms, respectively (Fig 5, *A*); respective investigator-reported response rates were higher (23.1% and 34.8%) (Fig 5, *B*). Disease control by central review was reported in 92.3% and 91.3% of patients treated with sonidegib 200 and 800 mg, respectively. Investigators reported disease control in 84.6% and 82.6% of patients in the 200- and 800-mg arms. Tumor shrinkage (by any modality) by central review was observed in 91.7% (200 mg) and 84.2% (800 mg) of patients (Supplemental Fig 2, *A* and *B*); investigators reported similar results (Supplemental Fig 2, *C* and *D*). By central review, median time to tumor response was 1.8 and 1.0 months in the 200- and 800-mg arms, respectively, and tumor responses were durable, with 4 of 5 responders maintaining an objective response (Table I). By central review, the Kaplan-Meier median duration of response was not reached in either arm; by investigator review, median duration of response was 17.7 and 10.2 months, respectively (Table I).

Safety

From the time of the primary analysis to the 12-month analysis, the median duration of exposure

Table I. Efficacy of sonidegib by treatment arm

Patients with laBCC	Sonidegib 200 mg once daily n = 66		Sonidegib 800 mg once daily n = 128	
	Primary Analysis*	12-mo Analysis†	Primary Analysis*	12-mo Analysis†
Time to tumor response‡				
Median (95% CI), mo				
Per central review	3.9 (3.6-4.2)	4.0 (3.8-5.6)	3.7 (2.6-3.8)	3.8 (3.7-5.5)
Per investigator review	1.9 (1.8-3.7)	2.5 (1.9-3.7)	1.9 (1.2-2.0)	1.9 (1.4-2.0)
Duration of response§				
Events//responders, n/n; median (95% CI), mo				
Per central review	4/31; not reached	7/38; not reached	3/45; not reached	11/56; 15.7 (NE)
Per investigator review	10/43; 20.2 (10.1-20.2)	14/47; 20.2 (NE)	10/73; not reached	17/74; 19.8 (15.7-20.5)
Progression-free survival¶				
Events//, n; median (95% CI), mo				
Per central review	7; not reached	11; 22.1 (NE)	10; not reached	22; 21.5 (NE)
Per investigator review	15; 16.6 (13.7-22.0)	19; 22.0 (NE)	17; not reached	26; 21.5 (NE)

Patients with mBCC	Sonidegib 200 mg once daily n = 13		Sonidegib 800 mg once daily n = 23	
	Primary Analysis*	12-mo Analysis†	Primary Analysis*	12-mo Analysis†
Time to tumor response‡				
Median (95% CI), mo				
Per central review	4.6 (1.8-7.4)	1.8 (NE)	1.0 (1.0-2.1)	1.0 (1.0-2.1)
Per investigator review	1.0 (0.9-3.7)	1.0 (0.9-3.7)	2.7 (1.0-5.6)	2.7 (1.0-5.6)
Duration of response§				
Events//responders, n/n; median (95% CI), mo				
Per central review	0/2; not reached	0/1; not reached	1/4; 8.3 (NE)	1/4; not reached
Per investigator review	0/3; not reached	1/3; 17.7 (NE)	1/8; 10.2 (NE)	3/8; 10.2 (NE)
Progression-free survival¶				
Events//, n; median (95% CI), mo				
Per central review	4; 13.1 (5.6-13.1)	6; 13.1 (5.6-16.9)	10; 7.6 (6.2-11.1)	11; 11.1 (NE)
Per investigator review	7; 13.1 (9.2-16.6)	8; 13.1 (9.2-18.6)	6; 13.3 (NE)	10; 14.3 (11.1-20.2)

CI, Confidence interval; *laBCC*, locally advanced basal cell carcinoma; *mBCC*, metastatic basal cell carcinoma; *NE*, not estimable.
*Data cutoff was June 28, 2013; median follow-up was 13.9 months.
†Data cutoff was December 31, 2013; median follow-up was 20.0 months.
‡Time from randomization to first observed response (complete response or partial response), based on responder data only.
§Time from first observed response (complete response or partial response) until disease progression or death as a result of any cause.
//Progressive disease or death as a result of any cause.
¶Time from randomization to first documented disease progression or death as a result of any cause.

increased in the 200-mg arm (8.9 [range, 1.3-21.4] vs 11.0 [range, 1.3-27.8] months) and remained similar in the 800-mg arm (6.5 [range, 0.3-19.1] vs 6.6 [range, 0.3-27.8] months). Among patients treated with sonidegib 200 and 800 mg, 68.4% and 43.3% of patients, respectively, remained on treatment for 8 months or longer.

The safety profile of sonidegib remained similar between the primary and 12-month analyses.[20] Nearly all patients (200 mg, 97.5%; 800 mg, 100%) experienced 1 or more adverse events. In general, the most common adverse events, including muscle spasms, alopecia, dysgeusia, nausea, increased creatine kinase, fatigue, weight loss, decreased appetite, myalgia, and vomiting, occurred less frequently in the 200- versus 800-mg arm (Fig 6). Increased creatine kinase was the most common grade 3/4 adverse event, occurring in 6.3% (200 mg) and 13.3% (800 mg) of patients. Dose adjustment or interruption because of adverse events was required in 38.0% and 64.0% of patients, and discontinuation because of adverse events occurred in 27.8% (200 mg) and 37.3% (800 mg) of patients. The most common adverse events leading to discontinuation

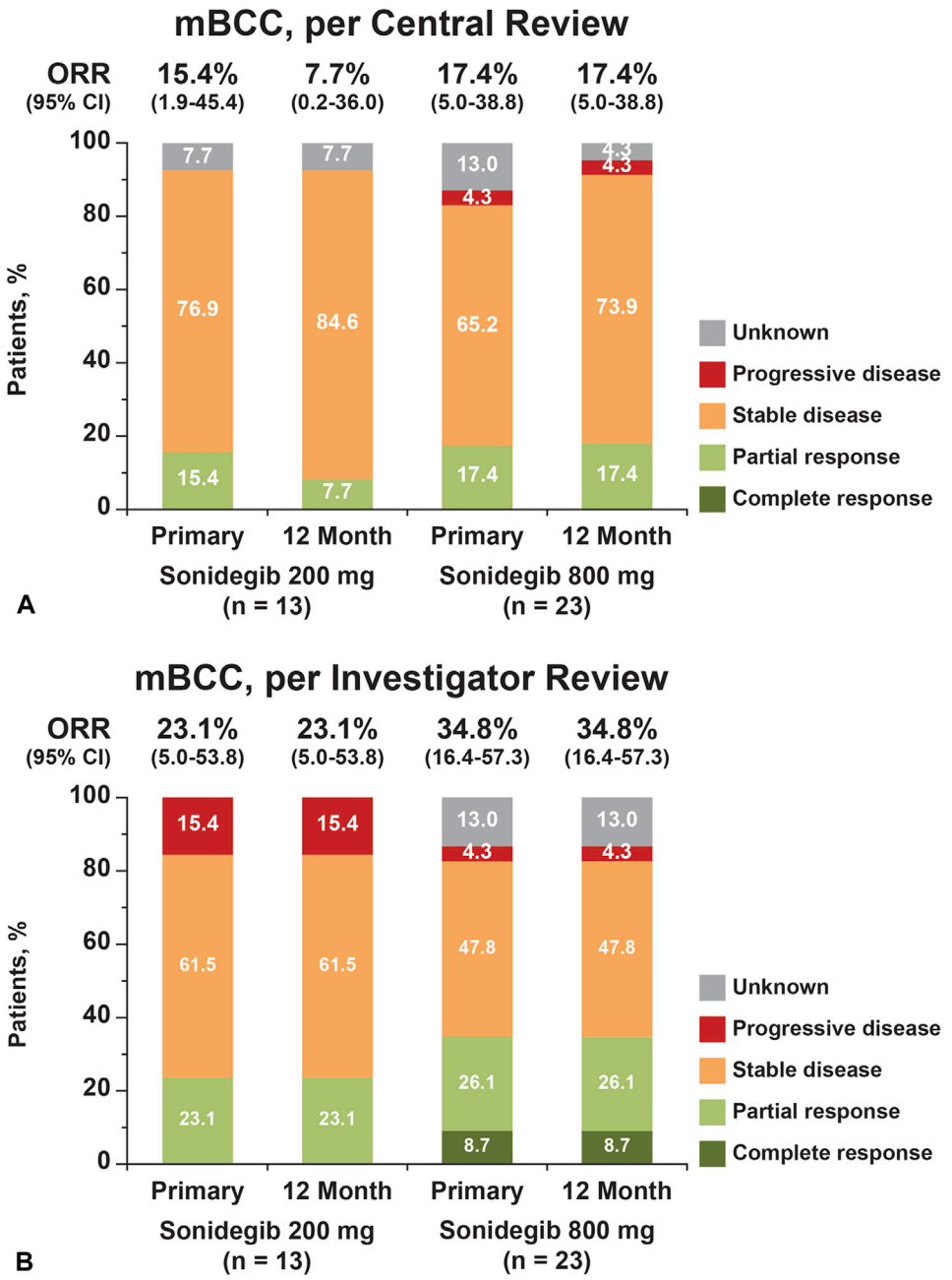

Fig 5. Objective response rates (ORRs) in patients with metastatic basal cell carcinoma (mBCC) treated with sonidegib 200 and 800 mg. Best overall response in patients with mBCC treated with sonidegib 200 mg (n = 13) and 800 mg (n = 23) assessed by computed tomography/magnetic resonance imaging per Response Evaluation Criteria in Solid Tumors v1.1[22] by central (**A**) and investigator (**B**) review at the time of the primary and 12-month analyses. Complete and partial responses required confirmation on repeated assessments at visits greater than or equal to 4 weeks apart. Best overall response of 1 patient changed from partial response to stable disease in the 12-month analysis by central re-review because of identification of a new lesion in a photograph received after the cutoff for the primary analysis (June 28, 2013).

(200- vs 800-mg arm) in the 12-month analysis included muscle spasms (5.1% vs 8.7%), dysgeusia (3.8% vs 4.7%), nausea (3.8% vs 4.7%), and alopecia (1.3% vs 6.0%); 59% of patients who discontinued treatment because of adverse events had only grade 1/2 events. Serious adverse events regardless of

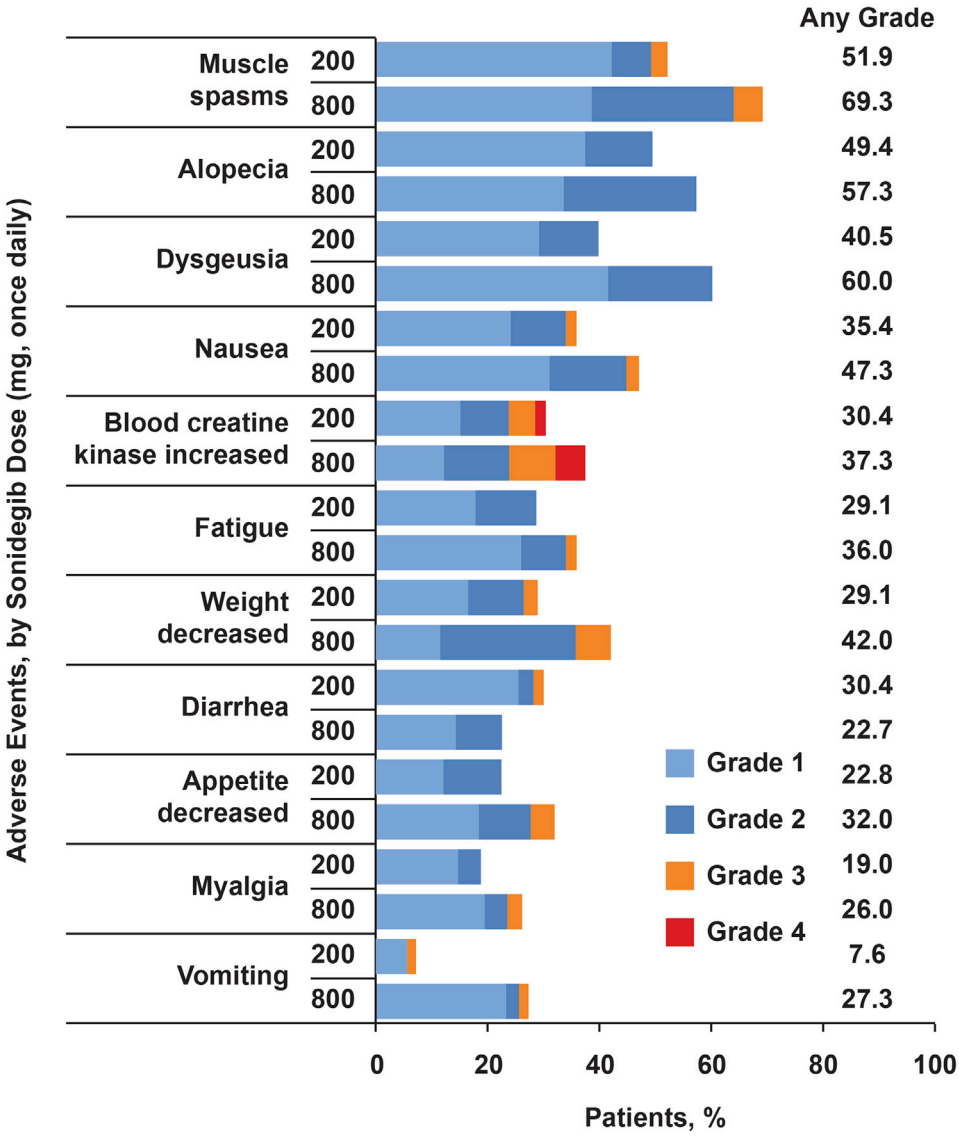

Fig 6. Advanced basal cell carcinoma. Most common adverse events, irrespective of causality, reported in more than 20% of patients overall. Adverse events reported in patients treated with sonidegib 200 mg (n = 79) and 800 mg (n = 150) were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 guidelines[23] and include adverse events occurring while on treatment and within 30 days of study drug discontinuation. A patient with multiple occurrences of an adverse event is counted only once in the category for that event, with the maximum severity rating reported. Adverse events are reported by grade.

causality occurred in 16.5% (200 mg) and 32.7% (800 mg) of patients; those suspected to be related to sonidegib treatment occurred less frequently (200 mg, 2.5%; 800 mg, 14.0%). Rhabdomyolysis (1.3% vs 3.3%) and increased creatine kinase (1.3% vs 2.7%) were the most common serious adverse events (200 vs 800 mg) reported by investigators in the 12-month analysis. None of the cases of rhabdomyolysis were confirmed by an independent review and adjudication committee of experts on muscle toxicity because renal function was not impaired in these patients.[20] At the time of data cutoff, 7 on-treatment deaths had occurred, 3 of which occurred after the primary analysis. All deaths occurred in the 800-mg arm and none were considered to be related to treatment. The 3 new deaths included 1 patient with laBCC with preexisting confounding conditions at baseline, who died of cardiac arrest (study day

349), and 2 patients with mBCC, who died of sepsis (day 391) and respiratory arrest (day 433).

DISCUSSION

BOLT met its primary end point of ORR per central review in both the 200- and 800-mg arms at the time of the primary analysis[20]; with the additional 6 months of follow-up in this 12-month analysis, sonidegib exhibited sustained efficacy in patients with advanced BCC. Response rates improved in patients with laBCC and remained similar in patients with mBCC in both treatment arms. In patients with laBCC, rates of response and disease control were numerically higher in the 200-mg arm than in the 800-mg arm likely because of the better tolerability and longer duration of exposure observed in patients treated with the 200-mg dose of sonidegib. Disease control and tumor shrinkage were observed in most patients with laBCC and mBCC. In patients with laBCC, tumor responses per central review were durable, with only 18 of 94 responders progressing. With longer follow-up, most patients were still alive without disease progression. Efficacy of sonidegib was similar in patients with aggressive and nonaggressive histologic subtypes of laBCC.

The BCC-mRECIST tumor response criteria used in patients with laBCC in BOLT is very stringent. In a previously described prespecified analysis,[24,25] response in patients with laBCC was reassessed using BCC-RECIST-like criteria similar to those used in the ERIVANCE study of vismodegib.[26,27] The key distinction between the criteria is the stringency required to achieve a complete response: BCC-mRECIST required negative histology and a complete response (or equivalent) by all image modalities used in the assessment, whereas BCC-RECIST-like required negative histology and a complete or partial response by either magnetic resonance imaging or photograph.[24,25] This analysis showed that the complete response rate in the 200-mg arm by central review was higher with BCC-RECIST-like than with BCC-mRECIST (19.7% vs 4.5%), and the response rate was similar using both criteria (62.1% vs 57.6%). The difference in rates of complete response demonstrates the stringency of the response criteria used in BOLT and emphasizes the clinical efficacy observed in patients with laBCC treated with sonidegib.[24,25]

Sonidegib had an acceptable safety profile, with generally fewer adverse events in the 200-mg arm. Most adverse events with sonidegib treatment were grade 1/2 and were consistent with the safety profile of other HPIs.[19,26-38] Muscle-related adverse events, including muscle spasms and elevated creatine kinase, were frequently observed in BOLT and have been reported with vismodegib, suggesting it may be a class effect.[26-28,33,39,40] Importantly, comprehensive guidelines were developed during BOLT to monitor and manage muscle-related adverse events with dose adjustments/interruptions[20] and will be used in patients treated with sonidegib moving forward.

HPIs have demonstrated efficacy in patients with advanced BCC[20,26,27]; however, despite achieving a response, some patients discontinue treatment because of low-grade adverse events that cause significant discomfort.[20,26] In BOLT, over half of the patients who discontinued because of adverse events had only grade 1/2 events, with many of these patients having already benefited from treatment.[41] Developing plans to manage adverse events, as was done in BOLT for muscle-related adverse events, and educating patients on the importance of remaining on therapy after achieving a response may help increase duration on treatment and thus improve patient benefit. A deeper response with HPIs may also be achieved if used in combination with chemotherapies or other targeted agents (eg, immune modifiers[42]).

In the BOLT 12-month analysis, sonidegib continued to demonstrate sustained, clinically meaningful responses in patients with advanced BCC with no new safety concerns. These data, in addition to the results from the 12-month update of ERIVANCE,[27] indicate that the approved HPIs sonidegib and vismodegib provide durable responses and have a manageable safety profile, supporting a role for HPIs in the treatment of patients with advanced BCC. Future studies designed to assess how to optimize HPI therapy and to understand how best to incorporate HPIs into the current treatment algorithm for advanced BCC are warranted.

We thank the patients and their families, the study investigators, their clinical teams and the study site staff, and the members of the study committees. We also thank the Novartis BOLT clinical study team. We thank the independent data monitoring committee (Mark R. Pittelkow, Jürgen C. Becker, and Stephen L. George), the efficacy independent review (Vernon K. Sondak, James Grichnik, and Lawrence Schwartz), and the muscle safety review and adjudication committee (Robert S. Rosenson, Vinay Chaudhry, and Paul D. Thompson).

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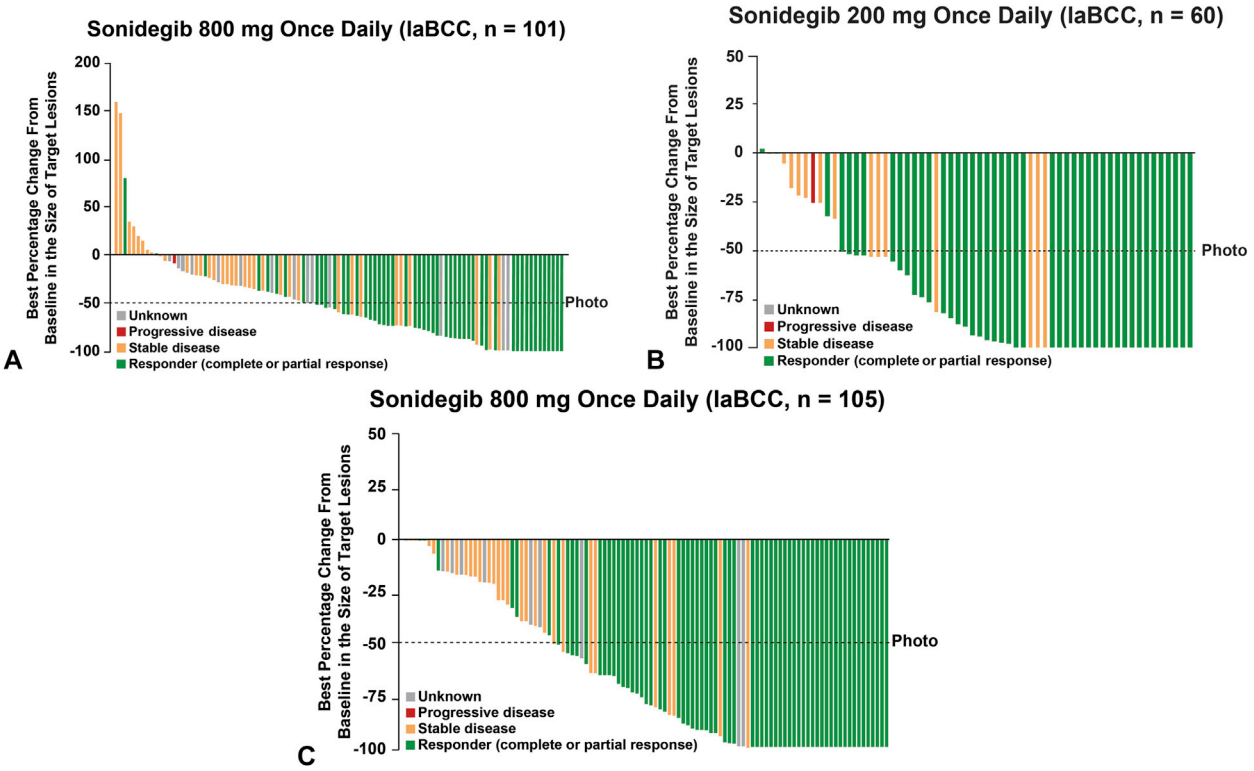
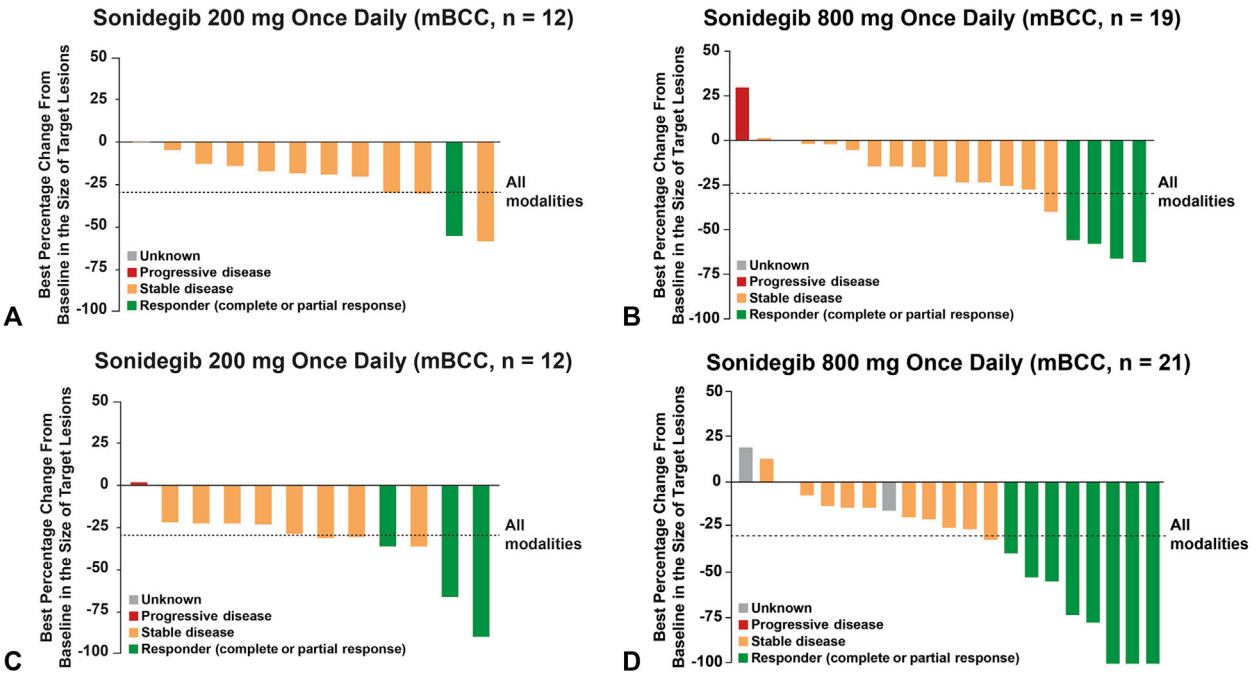


Supplemental Fig 1. Waterfall plots of best change from baseline in the size of target lesions in patients with locally advanced basal cell carcinoma (laBCC) per central review in the sonidegib 800-mg arm (**A**) and per investigator review in the sonidegib 200-mg arm (**B**) and 800-mg arm (**C**). Best percentage change from baseline in the sum of the products of perpendicular diameters in target lesion(s) assessed by photography per World Health Organization criteria[21] in the 800-mg arm (**A**) per central review and in the 200-mg arm (**B**) and 800-mg arm (**C**) per investigator review. Tumor response was assessed by photography, magnetic resonance imaging, and histology according to basal cell carcinoma–modified Response Evaluation Criteria in Solid Tumors in patients with laBCC, and best overall response is depicted by color. Assessments were excluded from the analysis if percentage change in the size of target lesions was not available or was contraindicated by an overall lesion response of unknown.



Supplemental Fig 2. Waterfall plots of best change from baseline in the size of target lesions in patients with metastatic basal cell carcinoma (mBCC) per central review in the sonidegib 200-mg arm (**A**) and 800-mg arm (**B**) and per investigator review in the sonidegib 200-mg arm (**C**) and 800-mg arm (**D**). Best percentage change from baseline in the sum of the longest diameters in target lesion(s) assessed by all modalities used in the evaluations (ie, computed tomography [CT] or magnetic resonance imaging [MRI]) per Response Evaluation Criteria in Solid Tumors v1.1[22] in the 200-mg arm (**A**) and 800-mg arm (**B**) per central review, and in the 200-mg arm (**C**) and 800-mg arm (**D**) per investigator review. Tumor response was assessed by CT/MRI in patients with mBCC, and best overall response is depicted by color. Assessments were excluded from the analysis if percentage change in the size of target lesions was not available or was contradicted by an overall lesion response of unknown.

Supplemental Table I. Composite overall response in locally advanced basal cell carcinoma determined by basal cell carcinoma–modified Response Evaluation Criteria in Solid Tumors

MRI*	Photograph†	Histology‡	Composite overall response§ BCC-mRECIST
CR	CR	Negative	CR‡
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative	
	Not available	Negative	
Not available	CR	Negative	CR‡
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative	
PR	CR	Negative	PR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative	
SD	CR	Negative	PR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative	
CR	CR	Positive or unknown	PR
	PR	Any	
	PR (scar/fibrosis only)	Positive or unknown	
	Not available		
PR	CR	Positive or unknown	PR
	PR	Any	
	PR (scar/fibrosis only)	Positive or unknown	
	Not available	Any	
SD	CR	Positive or unknown	PR
	PR	Any	
	PR (scar/fibrosis only)	Positive or unknown	
Not available	CR	Positive or unknown	PR
	PR	Any	
	PR (scar/fibrosis only)	Positive or unknown	
CR	SD	Any	SD
	SD (scar/fibrosis only)	Positive or unknown	
PR	SD	Any	SD
	SD (scar/fibrosis only)	Positive or unknown	
SD	SD	Any	SD
	SD (scar/fibrosis only)	Positive or unknown	
	Not available	Any	
Not available	SD	Any	SD
	SD (scar/fibrosis only)	Positive or unknown	
Any (except PD)	Unknown	Any	Unknown
Unknown	Any (except PD)	Any	Unknown
PD	Any	Any	PD
Any	PD	Any	PD

BCC, Basal cell carcinoma; *CR*, complete response; *MRI*, magnetic resonance imaging; *mRECIST*, modified Response Evaluation Criteria in Solid Tumors; *PD*, progressive disease; *PR*, partial response; *SD*, stable disease.

*Per Response Evaluation Criteria in Solid Tumors v1.1.[22]

†Per World Health Organization criteria.[21]

‡Required multiple biopsy specimens based on lesion surface area.

§An independent review committee re-evaluated all assessments for the locally advanced BCC cohort to determine a composite response.

Supplemental Table II. Patient demographics and disease history by treatment

Baseline characteristic*	Sonidegib 200 mg once daily n = 79	Sonidegib 800 mg once daily n = 151
Age, median (range), y	67 (25-92)	65 (24-93)
Sex, male, n (%)	48 (60.8)	96 (63.6)
Race, n (%)		
White	71 (89.9)	145 (96.0)
Other	8 (10.1)	6 (4.0)
Eastern Cooperative Oncology Group performance status, n (%)		
0	50 (63.3)	95 (62.9)
1	19 (24.1)	44 (29.1)
2	8 (10.1)	10 (6.6)
Unknown	2 (2.5)	2 (1.3)
Predominant histologic/cytologic subtype for all patients based on case report forms, n (%)		
Aggressive†	40 (50.6)	76 (50.3)
Nonaggressive‡	38 (48.1)	68 (45.0)
Undetermined	1 (1.3)	6 (4.0)
Missing	0	1 (0.7)
Predominant histologic/cytologic subtype for patients with laBCC based on randomization stratification, n (%)	n = 66	n = 128
Aggressive†	37 (56.1)	75 (58.6)
Nonaggressive‡	29 (43.9)	53 (41.4)
Metastasis, n (%)	14 (17.7)	23 (15.2)
Metastatic sites, n (% of total with metastasis)		
Lung	10 (71.4)	12 (52.2)
Lymph nodes§	1 (7.1)	7 (30.4)
Bone	2 (14.3)	5 (21.7)
Other//	3 (21.4)	7 (30.4)
Prior antineoplastic therapy, n (%)		
Surgery	60 (75.9)	127 (84.1)
Radiotherapy	19 (24.1)	49 (32.5)
Reason for enrollment, n (%)¶		
Multiple tumor recurrence after surgery or radiotherapy	15 (19.0)	47 (31.1)
Radiotherapy contraindicated because of preexisting condition	1 (1.3)	4 (2.6)
Surgery or radiotherapy inappropriate because of location of lesion	33 (41.8)	44 (29.1)
Severe disfigurement expected with surgical resection	25 (31.6)	43 (28.5)
Other	5 (6.3)	12 (7.9)
Missing	0	1 (0.7)

laBCC, Locally advanced basal cell carcinoma.

*Patients were evenly distributed between treatment arms (200 vs 800 mg) with regard to geographic region: Europe (57.0% vs 55.0%), North America (36.7% vs 40.4%), and Australia (6.3% vs 4.6%).

†Includes micronodular, infiltrative, multifocal, basosquamous, and sclerosing basal cell carcinoma.

‡Includes nodular and superficial basal cell carcinoma.

§Includes axillary, parotid, submandibular, supraclavicular, and other.

//Includes trunk, brain, head, liver, neck, and upper extremities.

¶Each patient enrolled provided only 1 reason.

Supplemental Table III. Patient disposition

Parameter	200 mg n = 79	800 mg n = 151	All N = 230
Patients randomized, n (%)			
Treated	79 (100)	150 (99.3)	229 (99.6)
Untreated	0	1 (0.7)	1 (0.4)
Patients treated, n (%)			
Treatment ongoing*	21 (26.6)	29 (19.2)	50 (21.7)
Treatment discontinued	58 (73.4)	121 (80.1)	179 (77.8)
Primary reason for treatment discontinuation, n (%)			
Adverse event	20 (25.3)	52 (34.4)	72 (31.3)
Patient decision†	7 (8.9)	29 (19.2)	36 (15.7)
Progressive disease‡	23 (29.1)	15 (9.9)	38 (16.5)
Physician decision†	7 (8.9)	11 (7.3)	18 (7.8)
Loss to follow-up	1 (1.3)	4 (2.6)	5 (2.2)
Death	0	5 (3.3)	5 (2.2)
Nonadherence	0	4 (2.6)	4 (1.7)
Protocol deviation	0	1 (0.7)	1 (0.4)
Study evaluation after end of treatment phase			
Patients continued to the next phase of the trial, n (%)	42 (53.2)	72 (47.7)	114 (49.6)
Posttreatment follow-up	17 (21.5)	36 (23.8)	53 (23.0)
Survival follow-up	25 (31.6)	36 (23.8)	61 (26.5)

*Patients ongoing at the time of the 12-mo analysis (data cutoff: December 31, 2013).
†Decisions to withdraw by patient or physician were mostly because of adverse events.
‡More patients in the 200-mg arm were able to remain on treatment until disease progression because of improved tolerability.